II. REMARKS

Formal Matters

Claims 1-8 and 10-22 are pending after entry of the amendments set forth herein.

Claims 1-8, 10-14, 19, and 20 were examined and were rejected. Claims 15-18, 21, and 22 were withdrawn from consideration.

Claims 1 and 12-14 are amended. The amendment to claim 1 is merely editorial in nature. As such, no new matter is added by the amendment to claim 1. Support for the amendments to claims 12-14 is found throughout the specification, including, e.g., at paragraph 0096. Accordingly, no new matter is added by the amendments to claims 12-14.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Objection to the drawing

The drawing was objected to. The Office Action stated that figure must not be enumerated since there is only one figure.

Applicants provide herewith a Replacement Figure, which replaces Figure 1.

Objection to the specification

The specification was objected to. The Office Action stated that the brief description of the drawings should not refer to an enumerated figure as there is only one figure.

The specification is amended, as noted above, to refer to "the figure" instead of "Figure 1."

Claim Objections

Claims 11 and 18 were objected to.

Claim 11

The Office Action stated that the second "apoE" should be deleted.

Claim 11 was previously amended to delete the extra "apoE." See the amendment, filed on December 22, 2006 and responsive to the Office Action mailed October 6, 2006.

Claim 18

The Office Action stated that the second period at the end of the sentence should be deleted.

Claim 18 was previously amended to delete the extra period. See the amendment, filed on December 22, 2006 and responsive to the Office Action mailed October 6, 2006.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-9 and 11-14 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Claim 1

The Office Action stated that claim 1 recites in the preamble a method for diagnosing Alzheimer's disease (AD); and stated that the body of the claim does not recite a step of diagnosing, or how the diagnosis was made. The Office Action stated that it is not clear whether the mere presence of the carboxyl-terminal truncated apoE is indicative of Alzheimer's disease, or whether an increased level of carboxyl-terminal truncated apoE is indicative of AD. Applicants respectfully traverse the rejection.

It is noted that, in the amendment, filed on December 22, 2006 and responsive to the Office Action mailed October 6, 2006, claim 1 was amended to recite "the method comprising detecting a level of carboxyl-terminal truncated apoE in an aqueous biological sample from the individual, wherein a level of carboxyl-terminal truncated apoE **that is significantly higher than the level present in a normal control indicates that the individual has AD**." As such, this issue was already addressed.

Claim 5

The Office Action stated that the phrase "the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE" is not clear. The Office Action stated that it is not clear to what positions Applicant is referring. The Office Action stated that Applicant has not indicated whether the positions are determined starting from the amino terminus or the carboxyl terminus. Applicants respectfully traverse the rejection.

As explained in the amendment, filed on December 22, 2006 and responsive to the Office Action mailed October 6, 2006, it is standard in the art to number amino acids starting from the amino terminus of a protein. As such, those skilled in the art would understand that the phrase "the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE" means that the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, numbered from the amino terminus of apoE. As such, claim 5 need not be amended.

Applicants note page 12 of the instant Office Action states that "it is acknowledged that by "amino acids 244-260 of apoE", Applicant is referring to the amino acids 244-260 of apoE numbered from the amino terminus of apoE." Office Action, page 12. As such, this rejection may be withdrawn.

Conclusion as to the rejection under 35 U.S.C. §112, second paragraph

Applicants submit that the rejection of claims 1-9 and 11-14 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §103(a)

Claims 1-8, 10-14, 19, and 20 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Roses et al. (U.S. Patent No. 5,508,167; "Roses") in view of Huang et al. ((2001) *Proc. Natl. Acad. Sci. USA* 98:8838-8843; "Huang").

The Office Action stated:

1) Roses discloses a method for diagnosing AD, comprising detecting apoE in a biological sample;

2) Roses teaches detecting apoE4 rather than carboxyl-terminal truncated apoE;

3) Huang teaches that carboxyl-terminal truncated forms of apoE are found to be higher in patients with AD than in normal patients.

The Office Action concluded that it would have been obvious to modify the Roses method to diagnose a patient by detecting carboxyl-terminal truncated apoE. Applicants respectfully traverse the rejection.

Roses discusses methods of diagnosing AD. Roses discusses detecting apolipoprotein E4. Roses neither discloses nor suggests detecting carboxyl-terminal truncated apolipoprotein E (apoE).

Huang does not cure the deficiency of Roses. Huang does not disclose or suggest that carboxyl-terminal truncated apoE would be present in a biological sample other than brain, and thus could be detected in a diagnostic test for AD. Huang states that carboxyl-terminal truncated apoE is present in brains of AD patients. Huang, page 8839, column 2, first paragraph under "Results." Huang also states that carboxyl-terminal truncated apoE was detected in the lysates (not in the culture medium) of transfected Neuro-2a cells expressing apoE3 or apoE4. Huang, page 8840, column 1, first paragraph.

Huang further states that carboxyl-terminal truncated apoE is present in intracellular inclusions. Huang, page 8840, column 2; and Figure 2. Thus, from reading Huang, one skilled in the art would not conclude that carboxyl-terminal truncated apoE would be present outside the brain, or in an aqueous biological sample that would normally be obtained from a living individual. As such, Roses, alone or in combination with Huang, cannot render instant claims 1-8, 10-14, 19, and 20 obvious.

The Office Action stated that "because Roses et al. disclose that bodily fluids such as blood and cerebrospinal fluid as well as tissues contain apoE that can be used in diagnosing Alzheimer's disease, the skilled artisan would be suggested to detect in non-tissue samples also the carboxyl-terminated apoE as disclosed by Huang et al. as a marker for Alzheimer's disease." Office Action, page 13.

However, it cannot be reasonably concluded, from a disclosure that apoE4 can be detected in bodily fluids such as blood, that carboxyl-terminal truncated apoE would also be present in an aqueous biological sample such as blood or serum.

Indeed, as shown in Figures 1a and 1b of Huang, carboxyl-terminal truncated apoE was found associated with neurofibrillary tangles (NFT), which are insoluble, intracellular formations.

Huang reports that carboxyl-terminal truncated apoE is found intracellularly in Neuro-2a cells, in NFT-like inclusions. Huang concludes that the "truncated apoE probably escapes the secretory or the endosomal-lysosomal internalization pathway, enters the cytosol, and interacts with p-tau and pNF-H." Huang, bridging sentence, pages 8840-8841. In view of such a disclosure, those skilled in the art would not conclude that carboxyl-terminal truncated is secreted, and therefore would not conclude that carboxyl-terminal truncated apoE would likely be found in bodily fluids such as serum.

Furthermore, full-length apoE is produced by a number of cells, including brain cells, and liver cells. The fact that full-length apoE is found in serum was well known, and not surprising, given its production by liver cells. Full-length apoE produced by liver cells plays a role in the transport of, inter alia, lipoproteins.

Carboxyl-terminal truncated apoE, on the other hand, was not disclosed as being produced outside the brain. In view of the fact that Huang discloses that carboxyl-truncated apoE is found in the brain, those skilled in the art would not conclude that carboxyl-truncated apoE would be found in fluids such as serum.

Indeed, it has been subsequently shown that carboxyl-truncated apoE is produced in neurons, but not by astrocytes. Brecht et al. (2004) *J. Neurosci.* 24:2527. There is no evidence in Roses or in Huang, or anywhere else in the literature, that carboxyl-truncated apoE would be produced outside the brain, and thus would be found in fluids such as serum.

Conclusion as to the rejection under 35 U.S.C. §103(a)

Applicants submit that the rejection of claims 1-8, 10-14, 19, and 20 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-281.

Respectfully submitted,
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Date: March 17, 2008

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